

WHAT IS CLAIMED IS:

1. A complex peptide mixture, comprising a plurality of peptides having a length within the range of 8 to 20 amino acids, wherein said mixture comprises peptides having a degree of diversity at defined positions in the peptide chain, wherein the degree of diversity in at least one defined position is different from the degree of diversity in at least one other defined position, and wherein in a majority of the mixture, the peptides include in at least four positions all of A, E, K, and Y and no other amino acids.
2. The peptide mixture of Claim 1, wherein in at least one position, a majority of the peptides in the mixture include each of one or two amino acids and no other amino acids.
3. The peptide mixture of Claim 1, wherein the amino acids in said at least four positions include all of A, E, K, and Y and no other amino acids in at least 75% of the peptides in the mixture.
4. The peptide mixture of Claim 1, wherein the amino acids in said at least four positions include all of A, E, K, and Y and no other amino acids in at least 90% of the peptides in the mixture.
5. The peptide mixture of Claim 1, wherein the amino acids in said at least four positions include all of A, E, K, and Y and no other amino acids in at least 95% of the peptides in the mixture.
6. The peptide mixture of Claim 1, wherein the amino acids in said at least four positions include all of A, E, K, and Y and no other amino acids in substantially all of the peptides in the mixture.
7. The peptide mixture of Claim 1, wherein a majority of the peptides in the mixture are acetylated at the N-terminal amino acid.
8. The peptide mixture of Claim 1, wherein the amino acids A, E, K, and Y in said at least four positions are present in the following molar proportions: about 6: about 2: about 5: about 1.
9. The peptide mixture of Claim 1, wherein in at least one position, a majority of the mixture consists of peptides that include all of I, L, and V and no other amino acids.
10. The peptide mixture of Claim 1, wherein in at least one position, a majority of the mixture consists of peptides that include all of H, R, and K and no other amino acids.

11. The peptide mixture of Claim 1, wherein in at least one position, a majority of the mixture consists of peptides that include all of K, H, R, and V and no other amino acids.

12. A complex peptide mixture, comprising a plurality of peptides having a length within the range of 8 to 20 amino acids, wherein said mixture comprises peptides having a degree of diversity at defined positions in the peptide chain and wherein at least in a majority of the mixture, the amino acids in the peptides include all of the following specified amino acids and no other amino acids:

in at least four positions: A, E, K, and Y;

in at least one position: I, L, and V;

in at least one position: H, R, and K; and

in at least one position: P and I.

13. The peptide mixture of Claim 12, wherein position P1 is the N-terminal residue.

14. The peptide mixture of Claim 12, wherein the N-terminal residue is acetylated.

15. The peptide mixture of Claim 12, wherein A, E, K, and Y are present in at least four of positions P1, P2, P3, P4, P6, and (if present), P9.

16. The peptide mixture of Claim 12, wherein said peptides have a length of at least 10 amino acids and A, E, K, and Y are present in all of positions P1, P2, P3, P4, P6, and P9.

17. The peptide mixture of any of Claims 12, 15, or 16, wherein the amino acids A, E, K, and Y in said at least four positions are present in the following molar proportions: about 6: about 2: about 5: about 1.

18. The peptide mixture of Claim 12, wherein at least in a majority of the mixture, the amino acids in the peptides include all of the following specified amino acids and no other amino acids in at least one position: K, H, R, and V.

19. The peptide mixture of Claim 12, wherein at least in a majority of the mixture, the amino acids at the carboxy terminus of the peptides include both P and I and no other amino acids.

20. The peptide mixture of Claim 12, wherein a majority of the peptides in the mixture have, in at least one position, the same amino acid.

21. The peptide mixture of Claim 12, wherein substantially all of the peptides in the mixture have, in at least one position, one or the other of two selected amino acids.

22. The peptide mixture of any of Claims 12-21, wherein the N-terminal amino acid is acetylated.

23. Use of a complex peptide mixture in the preparation of a medicament for treating a disease, by administering to a vertebrate said complex peptide mixture, wherein said mixture comprises peptides having a constrained degree of diversity at each of at least 4 defined positions in the peptide chain and wherein the constrained degree of diversity in at least one defined position is different from the constrained degree of diversity in at least one other defined position.

24. The use of Claim 23, wherein the peptides in said mixture are from about 8 to about 20 amino acids in length, and wherein the N-terminal peptide is acetylated.

25. The use of Claim 23, wherein at least in a majority of the mixture, the amino acids in the peptides include all of the following specified amino acids and no other amino acids:

in at least four positions: A, E, K, and Y;

in at least one position: I, L, and V;

in at least one position: H, R, and K.

26. The use of Claim 25, wherein at least in a majority of the mixture, the amino acids in the peptides include all of the following specified amino acids and no other amino acids in at least one position: K, H, R, and V.

27. The use of Claim 25, wherein at least in a majority of the mixture, the amino acids at the carboxy terminus of the peptides include both P and I and no other amino acids.

28. The use mixture of Claim 25, wherein the amino acids A, E, K, and Y in said at least four positions are present in the following molar proportions: about 6: about 2: about 5: about 1.

29. The use of Claim 25, wherein a majority of the peptides in the mixture have, in at least one position, the same amino acid.

30. The use of Claim 25, wherein substantially all of the peptides in the mixture have, in at least one position, the same amino acid.

31. The use of Claim 25, wherein said disease is selected from the group consisting of multiple sclerosis and experimental autoimmune encephalomyelitis.

32. Use of a complex mixture of peptides in the preparation of a medicament for stimulating an immune cell by administration to of said complex peptide mixture to said cell, wherein said mixture comprises peptides having a constrained degree of diversity at each of at least 4 defined positions in the peptide chain, and wherein the degree of diversity in at least one defined position is different from the degree of diversity in at least one other defined position.

33. The use of Claim 32, wherein the constrained degree of diversity is created by limiting the possible amino acids at each of the said defined positions to a defined list of amino acids that includes less than 10 amino acids.

34. The use of Claim 32, wherein said stimulating of an immune cell occurs in vivo.

35. The use of Claim 32, wherein said administering step is selected from the group consisting of intravenous delivery, intramuscular delivery, delivery via the gastrointestinal tract, and transdermal delivery.

36. Use of a complex peptide mixture in the preparation of a medicament for suppression of an immune reaction to an antigen, by administering said complex peptide mixture to an individual, said complex peptide mixture comprising peptides having a constrained degree of diversity at each of at least 10 defined positions in the peptide chain, and wherein the degree of diversity in at least one or two defined positions is different from the degree of diversity in at least one or two other defined positions.

37. The use of Claim 36, wherein said immune reaction is an autoimmune reaction.

38. The use of Claim 37, wherein said antigen is derived from myelin.

39. The use of Claim 36, wherein said peptide complex mixture comprises peptides of a defined length and formula comprising at least one position with a specific amino acid and at least one position with two to six possible amino acids.

40. The use of Claim 36, wherein said peptide complex mixture is a less-diverse subset of a complex mixture having a higher degree of diversity.

41. The use of Claim 36, wherein said complex mixture with a higher degree of diversity is a mixture whose formula is selected from the group consisting of the formulas listed in Table 1.

42. The use of Claim 36, wherein the activity of said peptide complex mixture is evaluated by an assay selected from the group consisting of a proliferation assay, a cytokine assay and a  $^{51}\text{Cr}$  release assay.

43. The use of Claim 38, wherein said suppression of an autoimmune reaction to myelin proteins is due to a mechanism selected from the group consisting of MHC blockade, TCR antagonism, tolerance induction, immune deviation/bystander suppression and cross reactivity with an antigen derived from a protein expressed within the central nervous system.

44. The use of Claim 38, wherein said myelin antigen is derived from a protein selected from the group consisting of myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein.

45. The use of Claim 36, wherein said antigen is derived from a protein expressed by a cell found in the central nervous system.

46. Use of a complex peptide mixture in the preparation of a medicament for inducing an anti-inflammatory response from immune system cells, by administering said complex peptide mixture to immune system cells, said complex peptide mixture comprising peptides having a constrained degree of diversity at each of at least 10 defined positions in the peptide chain, and wherein the constrained degree of diversity in at least one or two said defined positions is different from the degree of diversity in at least another defined position.

47. The use of Claim 46, wherein said anti-inflammatory response comprises an alteration in immune cell activity selected from the group consisting of an upregulation of Th2/Th3 cell activity and a downregulation of Th1 cell activity.

48. The use of Claim 46, wherein said anti-inflammatory response comprises an increase in the release of cytokines by cells, said cytokines selected from the group consisting of IL-4, IL-5, IL-10, TGF-beta and IL-13.

49. The use of Claim 46, wherein said inducing of an anti-inflammatory response occurs in vivo.

50. The use of Claim 49, wherein said administration is performed by a method selected from the group consisting of intravenous delivery, intramuscular delivery, delivery via the gastrointestinal tract, and transdermal delivery.

51. A method for creating a high affinity peptide ligand of a defined formula for a receptor of a T cell that is reactive to a myelin antigen, copolymer or an active mixture,



comprising the deconvolution of a complex peptide mixture of a formula selected from the group consisting of the formulas listed in Table 1.

52. A complex peptide mixture, wherein said mixture comprises peptides between 4 and 100 amino acid residues in length, wherein said mixture has a constrained degree of diversity at each of at least 10 defined positions in the peptide chain, and wherein the degree of diversity in at least one defined position is different from the degree of diversity in at least one other defined position.

53. The complex peptide mixture of Claim 52, wherein the constrained degree of diversity is created by limiting the possible amino acids at each of the said defined positions to a list of possible amino acids that includes less than 10 amino acids.

54. The complex peptide mixture of Claim 53, wherein the list of possible amino acids for at least two of the said defined positions includes only 1, 2, or 3 amino acids.

55. The complex peptide mixture of Claim 52, wherein a majority of the peptides in the mixture have a length between about 4 and about 30 amino acid residues.

56. The complex peptide mixture of Claim 52, , wherein a majority of the peptides in the mixture vary in length by no more than 4 amino acid residues.

57. The complex mixture of Claim 52, wherein a majority of the peptides in the mixture are acetylated.

58. The complex mixture of Claim 52, wherein at least one position of one peptide in the mixture is occupied by a D-amino acid.

59. A method of enhancing a biological property of a complex mixture of peptides, peptidomimetics, or peptides and peptidomimetics, comprising:

providing a set of complex mixtures of reduced complexity that have a reduced degree of diversity from said complex mixture at least at one position;

testing each of said complex mixtures of reduced complexity and said complex mixture in an assay;

identifying complex mixtures of reduced complexity that have a greater or lesser activity in said assay than said complex mixture; and

enhancing the biological property of said complex mixture by incorporating the complexity-reducing features of at least one of said complex mixtures of reduced complexity that have greater or lesser activity in said assay than said complex mixture into the formula of said complex peptide mixture.

60. The method of Claim 59, wherein said biological property is selected from the group consisting of the ability to stimulate an immune system activity and the ability to suppress an immune system activity.

61. The method of Claim 60, wherein said immune system activity is selected from the group consisting of the clonal expansion of an immune system cell, the differentiation of an immune system cell, the activation of an immune system cell, the creation of an anergic state in an immune system cell, the creation of a memory immune cell population and the secretion of cytokines from an immune system cell.

62. The method of Claim 59, wherein said complex mixtures of reduced complexity comprise mixtures where the identity of the residue or amino acid in one or more positions in the mixture formula is limited to one functionality or amino acid.

63. The method of Claim 59, wherein said complex mixtures of reduced complexity comprise mixtures wherein the identity of the residue or amino acid in one or more positions in the mixture formula is limited to a formula less diverse than the formula for that position in said complex mixture of peptides, peptidomimetics, or peptides and peptidomimetics.

64. The method of Claim 59, wherein said assay is selected from the group consisting of an *in vitro* assay of peptide, peptidomimetic, or peptides and peptidomimetics recognition by an immune cell population and an assay of the effects of mixture administration on an organism.

65. The method of Claim 64, wherein said assay of the effects of mixture administration on an organism is an assay of disease progression in the EAE mouse model.

66. The method of Claim 59, wherein enhancing the biological activity of said complex mixture of peptides, peptidomimetics, or peptides and peptidomimetics comprises the limiting of the identity of the amino acid or residue at a position in the compound formula to a single amino acid or functionality.

67. A complex peptide mixture, comprising a plurality of peptides having a length within the range of 8 to 20 amino acids, wherein said mixture comprises peptides having a degree of diversity at defined positions in the peptide chain, and wherein at least in a majority of the mixture, the identity of 10 contiguous amino acids in the peptides are defined by the following formulas: FW-EF-EK-AEK-AKY-ANY-ANY-AINV-ASV-Y; or EFWY-EFIVWY-EFKQ-AEKQ-AKQY-ANQY-AGNSY-AGINSV-AIQSV-IKRSVY.

68. The peptide mixture of Claim 67, wherein position P1 of the 9 contiguous amino acid residues is the N-terminal peptide.

69. The peptide mixture of Claim 67, wherein the N-terminal amino acid is acetylated.

70. The peptide mixture of Claim 12, wherein a majority of the peptides in the mixture have, in at least one position, the same amino acid.

71. The peptide mixture of Claim 12, wherein substantially all of the peptides in the mixture have, in at least one position, the same amino acid.

72. A complex peptide mixture, comprising a plurality of peptides having a length within the range of 8 to 20 amino acids, wherein said mixture comprises peptides having a degree of diversity at defined positions in the peptide chain, wherein the degree of diversity in at least one defined position is different from the degree of diversity in at least one other defined position, wherein in a majority of the mixture, the peptides include in at least one but no more than five positions all of A, E, K, and Y and no other amino acids.

73. The peptide mixture of Claim 72, wherein in at least one position, a majority of the peptides in the mixture include each of one or two amino acids and no other amino acids.

74. The peptide mixture of Claim 72, wherein the amino acids in said at least one but no more than five positions include all of A, E, K, and Y and no other amino acids in at least 75% of the peptides in the mixture.

75. The peptide mixture of Claim 72, wherein the amino acids in said at least one but no more than five positions include all of A, E, K, and Y and no other amino acids in at least 90% of the peptides in the mixture.

76. The peptide mixture of Claim 72, wherein the amino acids in said at least one but no more than five positions include all of A, E, K, and Y and no other amino acids in at least 95% of the peptides in the mixture.

77. The peptide mixture of Claim 72, wherein the amino acids in said at least one but no more than five positions include all of A, E, K, and Y and no other amino acids in substantially all of the peptides in the mixture.

78. The peptide mixture of Claim 72, wherein a majority of the peptides in the mixture are acetylated at the N-terminal amino acid.



79. The peptide mixture of Claim 72, wherein the amino acids A, E, K, and Y in said at least one but no more than five positions are present in the following molar proportions: about 6: about 2: about 5: about 1.

80. The peptide mixture of Claim 72, wherein in at least one position, a majority of the mixture consists of peptides that include all of I, L, and V and no other amino acids.

81. The peptide mixture of Claim 72, wherein in at least one position, a majority of the mixture consists of peptides that include all of H, R, and K and no other amino acids.

82. The peptide mixture of Claim 72, wherein in at least one position, a majority of the mixture consists of peptides that include all of K, H, R, and V and no other amino acids.

83. The method of Claim 59, wherein said biological property is the response measured in an in vivo model of disease.

84. The method of Claim 83, wherein said in vivo model is selected from the group comprising a model of anxiety, depression, obesity, cognition, neurological disorder, motor disorder, or pain..